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- (51) International Patent Classification⁷: **A61K 9/08**, 35/78, 31/60, A61P 29/00 (74) Agent: **COCKBAIN, Julian**; Frank B. Dehn & Co., 179 Queen Victoria Street, London EC4V 4EL (GB).
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- (75) Inventors/Applicants (*for US only*): **STEEN-FELDT-FOSS, Henrik** [NO/NO]; c/o Norway Medical Group Int. AS, Møllerveien 4, N-0182 Oslo (NO). **THRANE, Per, Stanley** [NO/NO]; c/o Norway Medical Group Int. AS, Møllerveien 4, N-0182 Oslo (NO). **KLAVENESS, Jo** [NO/NO]; c/o Norway Medical Group Int. AS, Møllerveien 4, N-0182 Oslo (NO).
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: USE

(57) Abstract: The invention provides an alcoholic solution of a physiologically tolerable salicylic acid derivative and an acemannan for use in topical treatment of herpetic neuralgia. The invention also provides a method of treatment of herpetic neuralgia in a human subject which comprises applying an analgesically effective amount of such a solution to the affected area.

WO 02/45687 A2

Use

This invention relates to the use of topically applied salicylic acid derivative compositions in the treatment of herpes zoster in humans, in particular to the use of such compositions which are in liquid form and which further contain aloe vera or acemannan, an active component thereof.

The virus herpes zoster is a latent form of the virus responsible for chicken pox and causes the intractable and painful skin eruptions known as shingles which afflict many millions of the elderly in particular. Such painful occurrences are known as herpetic neuralgia, e.g. acute herpetic neuralgia and postherpetic neuralgia.

Aspirin, acetyl salicylic acid (ASA), is a very well known anti-inflammatory which is normally administered orally in tablet form. While liquid compositions containing ASA, in particular alkanolic solutions of ASA, have been proposed, e.g. for treatment of muscle and joint pain, rheumatism, etc, in recent years liquid ASA formulations have fallen out of favour since ASA is susceptible to hydrolysis producing the irritant salicylic acid.

We have now found that topically applied alcoholic solutions of ASA and acemannan are surprisingly effective in combatting herpetic neuralgia, in particular providing a level of pain relief to the patient.

Thus viewed from one aspect the invention provides an alcoholic solution of a physiologically tolerable salicylic acid derivative and an acemannan for use in topical treatment of herpetic neuralgia.

Viewed from a further aspect the invention provides the use of a physiologically tolerable salicylic acid derivative, an alcohol and an acemannan for the

manufacture of a topically applicable medicament for use in the treatment of herpetic neuralgia.

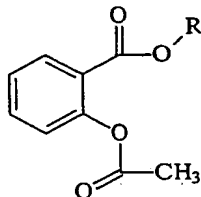
Viewed from a still further aspect the invention provides a method of treatment of herpetic neuralgia in a human subject which method comprises applying to an affected area of the skin of said subject an analgesically effective amount of an alcoholic solution of a physiologically tolerable salicylic acid derivative and an acemannan.

The salicylic acid derivative used according to the invention may be any physiologically tolerable derivative having analgesic properties.

The salicylic acid derivative used in the present invention is preferably ASA, or a physiologically tolerable prodrug (e.g. glycolamide) or salt (e.g. a lysine salt) or ester form thereof or an analog thereof (e.g. a 4 or 5 substituted, for example a 4- and/or 5-nitro and/or methoxy acetyl salicylic acid).

The salicylic acid derivative, if used in salt form, will have as counterion a physiologically tolerable counterion, preferably an amino acid such as lysine. Other tolerable counterions include sodium and meglumine.

Suitable prodrug forms of ASA include esters which hydrolyse more rapidly *in vivo* than the acetyl group, e.g. compounds of formula



where R is $-\text{CH}_2-\text{N}$

$-\text{CH}_2\text{SOCH}_3$, $-\text{CH}_2\text{SO}_2\text{CH}_3$, $-\text{CH}_2\text{OOCCH}_3$, $-\text{CH}_2\text{CONR}_1\text{R}_2$, where R_1 is C_{1-3} alkyl and R_2 is C_{1-3} alkyl, 2-hydroxy-ethyl or

-CH₂CONH₂, e.g. -CH₂CON(CH₃)₂, -CH₂CON(C₂H₅)₂, -CH₂CON(iPr)₂, -CH₂CON(CH₃)CH₂CH₂OH and CH₂CON(CH₃)CH₂CONH₂.

Acetyl salicylic acid is especially preferred.

The topically applied compositions of the invention also contain acemannan, e.g. in the form of aloe vera. If aloe vera is used, it is preferably used in a pure gel state, although aloe vera in a slightly impure (e.g. at least 98% wt pure) may also be used. Acemannan as such may be used in place of aloe vera.

The compositions of the invention may be in any topically applicable administration form which does not require rubbing of the affected skin, e.g. solutions, emulsions, dispersions, liposomal compositions, sprays, etc. Preferably, the compositions are in the form of solutions or liposome dispersions, particularly solutions.

If desired, the compositions may contain transdermal uptake promoters, such as for example dimethylsulphoxide (DMSO), dimethylformamide, dimethylacetamide, cycloalkanones, etc. (see US-A-5164416 and EP-A-435436).

The compositions contain an alcohol solvent for the salicylic acid derivative, e.g. a C₁₋₆ alkanol, preferably a propanol, especially isopropanol.

The compositions of the invention preferably also contain a drying agent, e.g. an inorganic salt in anhydrous or partially hydrated form, so as to minimize the water content of the solvent phase.

The drying agent is preferably a porous material which take up water into its pores or by surface adsorption. Alternatively, it may adsorb water by reaction or by hydration of an anhydrous or partially hydrated form of a crystalline substance with stable hydrated forms. Thus it may for example be a zeolite, e.g. a zeolite with a pore size of 4Å or more, for example up to 10Å (or where methanol is used as a solvent, a pore size of 3Å). Preferably a zeolite

having a pore size of up to 6Å, more preferably up to 5Å, e.g. 3 to 4Å, will be used. Such zeolites are available commercially, e.g. from Fluka. However calcined silica, alumina or silica-alumina or modified starches (e.g. the hydrolysed starch graft copolymers proposed for use in diapers or used in gardening as water retainers - see also GB-A-2009201 and EP-A-74179), or anhydrous or partially hydrated salts, such as metal sulphates (e.g. magnesium sulphate or sodium sulphate) may alternatively be used. Water retainers, e.g. modified starches, developed in the 1980s by Henkel for diapers and sanitary pads (see the patent publications of Henkel), and now used in gardening, are typified by "soil-moist", available from Sinclair, Lincolnshire, UK. The water-adsorbers used should preferably be substantially water free when incorporated into the compositions of the invention. Particle size is preferably 10 to 4000 µm, especially 50 to 2000 µm.

The compositions of the invention further preferably contain a stabilizer, e.g. a polyol or polyalkylene oxide, for example glycerol, polyethyleneglycol, diethyleneglycol, triethyleneglycol, etc.

Where the compositions are in the form of liposome suspensions, the lipids used as the liposomal membrane forming molecules are typically phospholipids or hydrogenated phospholipids such as natural or synthetic phosphatidylcholines (lecithins) (PC), phosphatidylethanolamines (PE), lysolecithins, lysophosphatidylethanolamines, phosphatidylserines (PS), phosphatidylglycerols (PG), phosphatidylinositol (PI), sphingomyelins, cardiolipin, phosphatidic acids (PA), fatty acids, gangliosides, glucolipids, glycolipids, mono-, di or triglycerides, ceramides or cerebroside, e.g. liposome membrane forming compounds such as are described in WO-92/21017.

The membrane forming lipids may also comprise

polymerizable lipids, e.g. methacrylate lipids, thiol and disulphide lipids, dienoate lipids, styryl lipids and diacetylanic lipids as described by Johnston in Liposome Technology Vol. I, Gregoriades Ed., pages 123-129 (1983) and Singh in Phospholipid Handbook, Cevc Ed., Dekker, pages 233-291 (1993) and references therein. The use of polymerizable lipids in the formation of the liposomes provides one route for increasing liposome stability. Liposomal compositions may be prepared by conventional means, e.g. sonication of a composition comprising the salicylic acid derivative in solution in an alcohol, and the liposomal membrane forming material. After liposome formation, the continuous phase can if desired be replaced by a continuous phase essentially free of the salicylic acid derivative.

The compositions of the invention will generally be applied directly to the affected skin site, e.g. by spraying or gentle swabbing.

As the affected skin is often extremely tender, the compositions of the invention are especially preferably applied as sprayed solutions, e.g. from pump action or pressurized spray dispensers. Pressurized spray dispensers are especially preferable as access of moisture to the solution during storage before and after first use, and hence hydrolytic breakdown of the salicylic acid derivative, may be avoided. Compositions in this format are novel and form a further aspect of the invention. Viewed from this aspect the invention provides a pressurized spray dispenser containing: an essentially anhydrous alkanolic solution of a physiologically tolerable salicylic acid derivative; a propellant; and optionally but preferably an acemannan.

In such dispensers, the propellant will be a compound or compound mixture, generally one which is in gaseous form at one atmosphere pressure at 21°C. Halocarbon propellants, e.g. CFCs, may be used but non-halocarbons are preferred. Typical suitable propellants

include hydrocarbons such as propane and butane.

Thus the compositions of the invention are generally low viscosity, easily sprayed liquids, which can be applied without discomfort to the patient.

By "essentially anhydrous" it is meant that the water content of the alkanol solution is sufficiently low that hydrolysis of the salicylic acid derivative does not occur to a significant extent during storage, e.g. the water content is 2.0% wt or less, preferably 1.0% wt or less. Particularly preferably the compositions herein described are substantially free from water.

The compositions of the invention preferably contain 1 to 30% wt. salicylic acid derivative (preferably ASA), especially 3 to 20% wt, more especially 4 to 8% wt, particularly 4.5 to 7.0% wt. Aloe vera is preferably present at 0.1 to 4% wt, especially 0.4 to 2% wt, particularly 0.7 to 1.5% wt. The stabilizer, if present, is preferably present at 0.5 to 20% wt, especially 2 to 10% wt, more especially 3 to 6% wt. Glycerol is preferably used in this regard. The alcohol solvent (preferably anhydrous isopropanol) is preferably present at about 70 to 80% wt. These percentages are relative to the total weight of the composition excluding any drying agent. If a drying agent is used, this is preferably present at 1 to 20% wt, especially 5 to 15% wt relative to the total weight of the composition.

The compositions of the invention are preferably administered in dosages of the salicylic acid derivative of 0.005 to 5 mg/cm² skin, especially 0.01 to 1.0 mg/cm².

The compositions of the invention may if desired contain further active ingredients, e.g. antiviral agents, NSAIDs, prostaglandin biosynthesis inhibitors, pain relievers (e.g. lidocaine or other -caine local anaesthetics), antioxidants, pH modifying agents, skin treatment agents (e.g. α -hydroxy acids), antimicrobial

agents, preservatives, aromas, etc. The compositions however will generally preferably be substantially free from Lowry Bronsted acid components, non-alcohol organic solvents (e.g. ethers, halocarbons, etc.) and ointment bases, e.g. containing no more than 2% wt, preferably no more than 0.5% wt in total of such components. In a preferred embodiment the compositions of the invention are substantially free from ethers and/or halogenated hydrocarbons.

All documents referred to herein are hereby incorporated by reference.

The invention will now be described further with reference to the following non-limiting Examples:

EXAMPLE 1

Solution for administration from a pressurized spray dispenser

Acetyl salicylic acid	5.7 parts by weight
Isopropanol (anhydrous)	94.3 parts by weight

EXAMPLE 2

Solution for application by spraying

Isopropanol (anhydrous)	74.8 parts by weight
Glycerol	4.1 parts by weight
Acetyl salicylic acid	5.1 parts by weight
Aloe vera	0.85 parts by weight

EXAMPLE 3Solution for application by spraying

Isopropanol (anhydrous)	81 parts by weight
Glycerol	3 parts by weight
Triethanolamine salicylate	15 parts by weight
Aloe vera	1 part by weight

EXAMPLE 4Case 1

A solution according to the invention, including aloe vera was applied to a 61 year old male, with acute Herpes zoster in the T 3 dermatome, in a lot of pain. Before application, on a numeric rating scale (from 11-0, where 11 is great pain) he rated the pain to 7, after application the following hour, he rated it to 4. He applied it almost every hour the following 24 hours. The skin-inflammation was greatly reduced, and the pain was reduced on the NR3 to 2-3.

EXAMPLE 5Case 2

A solution according to the invention, excluding aloe vera was applied to a 30 year old female, with acute Herpes simplex on lip. She enjoyed total relief after about 15 minutes of application. The inflammation was gone totally after 24 hours. She had used the spray approximately every 2 hours.

EXAMPLE 6Case 3

A solution according to the invention, excluding aloe vera was applied to a 37 old female, with acute Herpes simplex on a Labia majora, in pain. After 20 minutes she enjoyed full relief of pain, but she had to apply the spray every hour in 6 hours to get continuous pain relief. The inflammation was totally gone after 25 hours.

Claims:

1. An alcoholic solution of a physiologically tolerable salicylic acid derivative and an acemannan for use in topical treatment of herpetic neuralgia.
2. A solution as claimed in claim 1 wherein the salicylic acid derivative is selected from: acetyl salicylic acid, a physiologically tolerable prodrug of acetyl salicylic acid, a salt of acetyl salicylic acid with a physiologically tolerable counterion, an ester form of acetyl salicylic acid or an analogue thereof.
3. A solution as claimed in either of the preceding claims comprising aloe vera as said acemannan.
4. The use of a physiologically tolerable salicylic acid derivative, an alcohol and an acemannan for the manufacture of a topically applicable medicament for use in the treatment of herpetic neuralgia.
5. The use as claimed in claim 4 wherein said medicament is administered by spraying.
6. A method of treatment of herpetic neuralgia in a human subject, which method comprises applying to an affected area of the skin of said subject an analgesically effective amount of a solution as claimed in any of claims 1 to 3.
7. A method as claimed in claim 6 wherein the solution is administered by spraying.
8. A method as claimed in either of claims 6 or 7 wherein the solution is administered in dosages of the salicylic acid derivative of 0.005-5 mg/cm² skin.

- 11 -

9. A method as claimed in any of claims 6 to 8 wherein said derivative is acetyl salicylic acid.

10. A pressurized spray dispenser containing: an essentially anhydrous alkanolic solution of a physiologically tolerable salicylic acid derivative; a propellant; and optionally but preferably an acemannan.

11. A pressurized spray dispenser as claimed in claim 10 which contains an acemannan.

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- (71) Applicant (for all designated States except US):
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KLAVENESS, Jo [NO/NO]; c/o Norway Medical Group Int. AS, Møllerveien 4, N-0182 Oslo (NO).
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(54) Title: TOPICAL ALCOHOLIC SOLUTION OF A SALICYLIC ACID DERIVATIVE AND ACEMANNAN

(57) Abstract: The invention provides an alcoholic solution of a physiologically tolerable salicylic acid derivative and an acemannan for use in topical treatment of herpetic neuralgia. The invention also provides a method of treatment of herpetic neuralgia in a human subject which comprises applying an analgesically effective amount of such a solution to the affected area.

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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 01/05380

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K9/08 A61K31/60 A61P29/00 A61K9/12 A61K47/36

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched, (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, MEDLINE, CHEM ABS-Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 736 126 A (VAN ENGELEN H WAYNE ET AL) 7 April 1998 (1998-04-07) column 1, line 29 - line 45 column 1, line 54 - column 2, line 17 column 4, line 10 - line 23 column 4, line 29 - line 61; claims; example 1	1-7,9-11
X	WO 93 21899 A (PROCTER & GAMBLE) 11 November 1993 (1993-11-11) examples 3,4	1,3

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "8" document member of the same patent family

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Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 00 78354 A (COCKBAIN JULIAN ;NORWAY MEDICAL GROUP INT AS (NO); KLAVENESS JO (N) 28 December 2000 (2000-12-28) page 2, paragraph 3 -page 3, paragraph 2 page 5, line 35 -page 6, line 3 page 7, line 9 - line 10; claims 1,2,15; figure 1; example 1 page 6, paragraph 4 ---	1-3,10, 11
A	US 4 219 548 A (RELLER HERBERT H) 26 August 1980 (1980-08-26) column 3, line 44 - line 59 column 4, line 49 - last line; claims; examples 1,2 ---	1-11
A	US 4 942 031 A (LEVIN ROBERT H) 17 July 1990 (1990-07-17) claims 1,5,8-10; example 18 ---	1-11
A	SWERDLOW M: "TOPICAL APPLICATIONS FOR PAIN THERAPY IN POST-HERPETIC NEURALGIA" PAIN CLINIC, VNU, UTRECHT, NL, vol. 6, no. 3, 1993, pages 153-156, XP001057955 ISSN: 0169-1112 page 153, line 17 - line 41 ---	1-11
A	EP 0 405 299 A (BENEDITTIS GIUSEPPE DE) 2 January 1991 (1991-01-02) page 2, line 21 - line 28 page 3, line 8 - line 26; claims ---	1-11
A	US 5 034 221 A (ROSEN STEVEN E ET AL) 23 July 1991 (1991-07-23) column 3, line 48 -column 4, line 14 column 5, line 38 - line 43 -----	1-11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 01/05380

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 6-9 are directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-9, 10 partially, 11

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-9, 10 partially, 11

An alcoholic solution of a salicylic acid derivative and acemannan for the treatment of herpetic neuralgia. And a pressurized spray dispenser with an alcoholic solution of a salicylic acid derivative, an acemannan and a propellant.

2. Claim : 10 partially

A pressurized spray dispenser with an alcoholic solution of a salicylic acid derivative and a propellant.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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